REMARKS

Claims 24-28 are pending in the Subject Application. Claims 11, 12, 14-17 and 19-23 have been previously cancelled, and claim 24, 25, 26 and 27 have been amended.

Applicants wish to thank the Examiner for his comments in the telephone conference of October 19, 2004, clarifying his position regarding the Advisory Action of October 12, 2004.

The Examiner noted that the wrong "status identifier" was used for claim 28. Applicants have, in the present response, addressed the "status identifier" objection raised by the Examiner, and submit that the Amendment presented herein conforms to accepted practice.

The Examiner maintained his allegation the term "organized" introduced in amended claims 24-28, changes the scope of the invention, necessitating a new search, and allegedly raising new 112 1st and 2nd paragraph issues. Applicants respectfully disagree.

The subject Application clearly provides literal support for the term "organized bone formation". On Page 25, lines 12-21 (please note underlined sections):

> "Four weeks after transplantation, in non-union radial sites into which were transplanted C3H-BMP2 cells, we observed a unique regeneration process, which included <u>well organized new growth of bone</u> and cartilage *within the boundaries of the fracture edges*. In addition, *a collar of differentiating and calcifying chondrocytes was formed around the original edge of the bone defect*.... In all of the other experimental groups, including the group that received collagen

> sponges carrying rhBMP-2 protein, any bone or cartilage observed was formed in a disorganized manner."

Applicants submit that the phrase "well organized, new growth of bone" provides written description for the phrase "organized bone formation". Further, Applicants contend that the examples by definition represent embodiments of the invention.

The Examiner has alleged that the "degree of organization" that satisfies the limitation of "organized functional bone formation" is unclear. Applicants disagree.

Applicants have clearly indicated on Page 25, italicized section in the paragraph cited above, that the level of organization is demonstrated by the examples provided. Organized bone formation occurs "within the boundaries of the fracture edges". Further, on Page 26, lines 12-14, the degree of organization is described as:

> "Following C3H-BMP-2 transplantation, bone and cartilage formed around the fracture edge appeared organized and oriented according to the original pattern of radial bone, thus better reconstructing its original structure".

One skilled in the art would necessarily understand that the claimed "organized bone formation" occurs at a site of bone infirmity, in an orientation according to the original pattern of radial bone, to better reconstruct its original structure, which produced the resulting functional bone.

Moreover, the term "organized" is an art recognized term. Applicants submit that the term "organized", as defined in the Merriam-Webster's Dictionary (10^{th} Edition, at page 819, the excerpt of which is attached hereto as Appendix 1), is "to cause to develop an organic structure, or to form into a coherent unity or functioning whole". Applicants have clearly demonstrated the formation of a coherent unity and functioning whole, in the bone formed as a result of implantation of ex-vivo cultured, MSC engineered to express BMP-2 (as described hereinabove, in reference to the excerpts from pages 25 and 26, *supra*).

The Examiner has alleged that the inclusion of the term "organized" changes the scope of the invention and necessitates a new search. Applicants respectfully disagree. Applicants submit that the term "organized" does not broaden the scope of the claims, and thus does not necessitate a new search.

Applicants also wish the Examiner to consider the following arguments (also set forth by the Applicants in a September 27, 2004 response to the June 15, 2004 Office Action, issued by the USPTO, which was not admitted by the Examiner):

REJECTION UNDER 35 U.S.C. 112:

In the Office Action, the Examiner alleged that the subject matter does not reasonably convey to one skilled in the art that the inventor at the time the Application was filed was in possession of the invention. In particular, the rejection was based on claims directed to mesenchymal stem cells.

Applicants respectfully disagree. Example 11 of the subject Application clearly demonstrates the successful use of ex-vivo C3H10T1/2 cells transformed/transduced with BMP-2, for implantation at a site of a bone infirmity, resulting in the formation of organized, functional, bone formation at the defect site, in particular along the defect edges. Applicants maintain that one skilled in the art would know and understand that C3H10T1/2 cells are representative of mesenchymal stem cells, and Applicants maintain the following references support that such knowledge was in possession of one skilled in the art, at the time of the filing of the Application. The references are:

1) Nakamura T, Aikawa T, Iwamoto-Enomoto M, Iwamoto M, Higuchi Y, Pacifici M, Kinto N, Yamaguchi A, Noji S, Kurisu K, Matsuya T, Maurizio P. Induction of osteogenic differentiation by hedgehog proteins. Biochem Biophys Res Commun. 1997 Aug 18; 237(2):465-9.

2) Ahrens M, Ankenbauer T, Schroder D, Hollnagel A, Mayer H, Gross G. Expression of human bone morphogenetic proteins-2 or -4 in murine mesenchymal progenitor C3H10T1/2 cells induces differentiation into distinct mesenchymal cell lineages. DNA Cell Biol. 1993 Dec; 12(10):871-80.

Thus, contrary to the Examiner's assertion, there is support in the specification as filed for the term "mesenchymal stem cell"

REJECTION UNDER 35 U.S.C. § 103:

In the Office Action, the Examiner rejected claims 24-26 under 35 U.S.C. § 103 as allegedly being unpatentable over Ahrens et al, in view of US Patent No. 5,763,416 and US Patent No. 6,048,964. The Examiner asserted that based on Ahrens et al, in view of US Patent No. 5,763,416 and US Patent No. 6,048,964, it would have allegedly been obvious to one of ordinary skill in the art to combine to make the claimed invention, that of preparing ex-vivo cultured stem cells transformed with BMP-2 for implantation at a site of a bone infirmity.

In response, Applicants traverse the rejection of claims 24-26 under 35 U.S.C. § 103. Applicants maintain that Ahrens et al, in view of US Patent No. 5,763,416 and US Patent No. 6,048,964, do not render the claimed invention obvious, nor would a person of ordinary skill in the art have had a reasonable and/or credible expectation of success in obtaining the instant claimed invention given the teachings of Ahrens et al, in view of US Patent No. 5,763,416 and US Patent No. 6,048,964. The Examiner has alleged that Bonadio discloses the use of bone progenitor cells transformed with a BMP for stimulating bone formation.

Applicants respectfully disagree. Applicants maintain that although Bonadio suggest the use of bone progenitor cells for stimulating bone formation, such a suggestion is merely speculative and not credible, in view of what Bonadio demonstrated, and the knowledge in the art at the time.

Bonadio demonstrates **only** direct gene transfer of a bone morphogenetic protein. Bondaio asserts that the constructs are targeted to progenitor cells, however, there is no credible support for such a contention, **nor is it likely** that direct transfer of a nucleic acid to a site of bone infirmity is **appreciably** taken up *in situ* by a bone progenitor cell. Applicants

submit in a Declaration herein (attached hereto as Appendix 2) that Bonadio **describes** the use of an adenoviral vector for gene transfer experiments for *in vivo* bone regeneration, however adenoviral vector uptake is mediated by the CAR receptor, whose expression has been shown to be drastically diminished, if not absent in hematopoietic progenitor cells, as compared to their differentiated counterparts. Hematopoieitic progenitor cells in fact, are more differentiated than mesenchymal stem cells, and therefore it is unlikely that an even less differentiated cell type will exhibit appreciable CAR expression. The Rebel et al article, as described in the Declaration, further indicates that gene transfer does not appreciably occur in cells, which have diminished CAR expression. Thus, in the absence of a demonstration to the contrary, one skilled in the art, would assume, based on the foregoing, that adenoviral transfer of a gene would not be successful in progenitor cells in situ.

Bonadio further describes the use of DNA-soaked sponges as another means of gene delivery, wherein the DNA is purportedly taken up by progenitor cells. Applicants submit additional articles, as described in the attached Declaration, indicating that less differentiated cells have less propensity toward DNA uptake, similar to adenoviral uptake, and therefore neither method described by Bonadio provides for appreciable uptake of a foreign DNA sequence by mesenchymal stem cells. Thus, one skilled in the art would not credibly believe that Bonadio could predict uptake of a construct in situ by progenitor or stem cells.

Further, the Examiner has alleged that the motivation to combine the Bonadio and Ahrens references need only take into account a reasonable expectation of success in treating a site of bone infirmity in a human through the use of cultured mesenchymal stem cells that overexpress BMP-2, and the fact that Applicants data demonstrates the presence of autocrine and paracrine effects such cells demonstrates the fact that these mechanisms are necessarily present. Applicants respectfully disagree. Applicants maintain that there is no motivation to combine these references with a reasonable expectation of success for inducing organized, functional bone formation **at a site of bone infirmity** in a human.

Though Bonadio describes that progenitor cells are targeted by his gene transfer methods, such a conclusion is not credible, in lieu of direct demonstration by Bonadio that such is the case, as much of the cell population targeted is not a stem or progenitor cell,

moreover, uptake of the DNA by such cells *in situ*, according to one skilled in the art is drastically reduced, such that Bonadio does not credibly provide a foundation that BMP gene transfer provides more than paracrine effects for healing a bone infirmity.

While Ahrens provides for in vitro responses of progenitor cells to **a group of osteoinductive compounds**, which include *inter-alia*, a BMP, Ahrens provides no basis for the likelihood that implantation of such cells, transduced only with a BMP-2 vector, *in vivo* will stimulate bone induction **at a site of bone infirmity**. Such a result is predicated on appropriate cell homing and orientation along the defect edges, a result which could not have been forseen, based on either Ahrens, or credibly considered, in view of Bonadio. Moreover, the combination of Bonadio and Ahrens could not have predicted the unexpected results of the claimed invention, the formation of organized, functional bone formation evidenced in the instant invention, nor do they render obvious the likelihood of such formation at a site of bone infirmity.

Further, Ahrens demonstrates differentiation of MSCs in vitro, and in fact, as described in the Declaration attached hereto (Appendix 2), mesenchymal stem cells, which are cultured and differentiated *in vitro* when implanted *in vivo*, do not form functional tissue, and lose their cell surface marker phenotype (De Bari C. et al., Arthritis Rheum. 2004 Jan; 50(1):142-50). Thus, in view of the art cited, Ahrens in combination with Bonadio do not credibly suggest that an ex-vivo cultured, BMP, much less a BMP-2 transduced/transformed mesenchymal stem cell will form organized, functional bone at a site of bone infirmity following implantation.

Applicants maintain that the presence of autocrine and paracrine effects of expressed bone morphogenesis protein 2 resulted in the enhanced, organized, functional bone formation **at the site of bone infirmity**. Applicants maintain that it would not be obvious to combine the teachings of Bonadio, which only credibly describes paracrine effects of BMP on bone formation alone, and Ahrens, which demonstrates autocrine effects of **a group of osteoinductive compounds** to arrive at enhanced, organized, functional bone formation at a site of bone infirmity. Applicants maintain that combining the references of Bonadio and Ahrens do not credibly suggest cultured, progenitor cells transformed/transduced with a

BMP-2 alone, would effectively form bone at a site of infirmity, much less, that such bone formed would be enhanced, and organized along defect edges, and providing functional bone, which could only be revealed by the claimed invention.

Moreover, Applicant's unexpectedly discovered that ex-vivo cultured mesenchymal stem cells transduced/transformed with BMP such as BMP-2 form greater amounts of bone, than what is achieved by direct gene transfer, the presence of the protein, or differentiated cells secreting BMP-2, and that the bone formation is oriented along defect edges. Applicants results demonstrate bone formation, qualitatively and quantitatively, via the implantation of ex-vivo cultured, BMP-2 transduced/transformed mesenchymal stem cells, at a site of bone infirmity. Thus, a method of inducing organized (as exemplified in the subject Application in Example 11, by orientation of the bone formation along defect edges), bone formation at a site of bone infirmity, is novel and unobvious in view of the art.

In addition, the Examiner has also rejected claim 27 in view of the above cited references, further in view of Wozney, under 35 USC 103.

Wozney describes expression of a BMP receptor for BMP-2 in cells responding to the growth factor. Applicants maintain, that since neither Bonadio nor Ahrens provide a credible basis for the use of ex-vivo cultured MSC transduced/transformed with BMP-2 alone, in inducing organized functional bone formation at a site of bone infirmity, then the engineering of such cells to further express a BMP receptor is not rendered obvious, in consideration of Wozney.

Bonadio **describes** the use of an adenoviral vector for gene transfer experiments for *in vivo* bone regeneration, however adenoviral vector uptake is mediated by the CAR receptor, whose expression has been shown to be drastically diminished, if not absent in hematopoietic progenitor cells, as compared to their differentiated counterparts. Ahrens provides for in vitro responses of progenitor cells to **a group of osteoinductive compounds**, which include *inter-alia,* a BMP, Ahrens provides no basis for the likelihood that implantation of such cells, transduced only with a BMP-2 vector, *in vivo* will stimulate bone induction **at a site of bone infirmity**. Moreover, the combination of Bonadio and Ahrens could not have predicted the

unexpected results of the claimed invention, the formation of organized, functional bone formation evidenced in the instant invention, nor do they render obvious the likelihood of such formation at a site of bone infirmity.

Thus, since Bonadio and Ahrens do not render obvious the methods of inducing functional bone formation via implanting ex-vivo cultured MSC transfected with BMP-2, Applicants maintain that Wozney, further in view of the two does not render obvious the engineering of such cells to further express a BMP receptor.

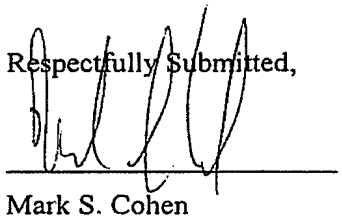
In addition the Examiner rejected claim 28 in view of the above cited references, further in view of Hattersley, under 35 USC 103. Hattersley describes the use of PTH and its receptor in the context of BMP-2. Applicants maintain, that Bonadio and Ahrens do not render obvious the methods of inducing functional bone formation via implanting ex-vivo cultured MSC transfected/transduced with BMP-2, and since the methods are not obvious in view of the art, neither is MSC expression of a PTH/PTH receptor. Therefore, Applicants submit that the additional reference does not render the instant invention obvious.

Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of the claims under 35 U.S.C. 103.

Accordingly, Applicants submit that the pending claims are allowable, and that Applicants have addressed all prior Rejections. Their favorable reconsideration and allowance is respectfully requested. Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below.

Should any fee be due, the undersigned Attorney hereby authorizes the United States Patent and Trademark Office to charge Deposit Account No. 05-0649 for any fees required.

Respectfully Submitted,



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pounds of living beings and most other carbon compounds **4 a** : forming an integral element of a whole : FUNDAMENTAL ⟨incidental music rather than ~ parts of the action —Francis Fergusson⟩ **b** : having systematic coordination of parts : ORGANIZED ⟨an ~ whole⟩ **c** : having the characteristics of an organism : developing in the manner of a living plant or animal ⟨society is ~⟩ **5** : of, relating to, or constituting the law by which a government or organization exists — **or·gan·i·cal·ly** \-ni-k(ə-)lē\ *adv* — **or·ga·nic·i·ty** \ˌȯr-gə-ˈni-sə-tē\ *n*

²organic *n* (1942) : an organic substance: as **a** : a fertilizer of plant or animal origin **b** : a pesticide whose active component is an organic compound or a mixture of organic compounds

or·gan·i·cism \ȯr-ˈga-nə-ˌsi-zəm\ *n* [ISV] (1883) **1 a** : the explanation of life and living processes in terms of the levels of organization of living systems rather than in terms of the properties of their smallest components **b** : VITALISM **2** : any of various theories that attribute to society or the universe as a whole an existence or characteristics analogous to those of a biological organism — **or·gan·i·cist** \-sist\ *n or adj*

or·ga·ni·sa·tion, or·ga·nise, or·ga·nis·er *Brit var of* ORGANIZATION, ORGANIZE, ORGANIZER

or·gan·ism \ˈȯr-gə-ˌni-zəm\ *n* (ca. 1774) **1** : a complex structure of interdependent and subordinate elements whose relations and properties are largely determined by their function in the whole **2** : an individual constituted to carry on the activities of life by means of organs separate in function but mutually dependent : a living being — **or·gan·is·mic** \ˌȯr-gə-ˈniz-mik\ *also* **or·gan·is·mal** \-məl\ *adj* — **or·gan·is·mi·cal·ly** \-mi-k(ə-)lē\ *adv*

or·gan·ist \ˈȯr-gə-nist\ *n* (1591) : a person who plays the organ

¹or·ga·ni·za·tion \ˌȯr-gə-nə-ˈzā-shən, ˌȯrg-nə-\ *n* (15c) **1 a** : the act or process of organizing or of being organized **b** : the condition or manner of being organized **2 a** : ASSOCIATION, SOCIETY ⟨charitable ~s⟩ **b** : an administrative and functional structure (as a business or a political party); *also* : the personnel of such a structure

²organization *adj* (1949) : characterized by complete conformity to the standards and requirements of an organization ⟨an ~ man⟩

or·ga·ni·za·tion·al \-shnəl, -shə-nᵊl\ *adj* (1881) **1** : of or relating to an organization : involving organization ⟨the ~ state of a crystal⟩ **2** : ORGANIZATION — **or·ga·ni·za·tion·al·ly** *adv*

or·ga·nize \ˈȯr-gə-ˌnīz\ *vb* **-nized; -niz·ing** *vt* (15c) **1** : to cause to develop an organic structure **2** : to form into a coherent unity or functioning whole : INTEGRATE ⟨trying to ~ her thoughts⟩ **3 a** : to set up an administrative structure for **b** : to persuade to associate in an organization; *esp* : UNIONIZE **4** : to arrange by systematic planning and united effort ~ *vi* **1** : to undergo physical or organic organization **2** : to arrange elements into a whole of interdependent parts **3** : to form an organization; *specif* : to form or persuade workers to join a union ***syn*** see ORDER — **or·gan·iz·able** \ˌȯr-gə-ˈnī-zə-bəl\ *adj*